Case Reports

Systemic Lupus Erythematosus Presenting as Hypoglycemia With Insulin Receptor Antibodies

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ANTIBODIES to the insulin receptor have been described in several diseases including diabetes mellitus with acanthosis nigricans,[1] Hashimoto's thyroiditis,[2] primary biliary cirrhosis,[3] progressive systemic sclerosis,[4] Sjögren's syndrome,[5] and systemic lupus erythematosus.[6-8] These antibodies have been shown to produce hyperglycemic episodes,[1,4,5,8] hypoglycemic episodes,[2,3,6,7] or both,[9,10] in a given patient. Rarely has an antibody to the insulin receptor with documented hypoglycemic episodes been described as a presenting symptom in a patient with systemic lupus erythematosus.[7]

Report of a Case

The patient, a 24-year-old woman, was referred for evaluation of hypoglycemia. She was nine months postpartum and had had episodes of extreme sleepiness, agitation, and drenching sweats that usually occurred between 7 and 9 AM. During one episode her plasma glucose level was recorded as 35 mg per dl,* and her symptoms resolved after she was given a solution of 50% dextrose in water intravenously. She said she had no other concurrent symptoms except for bilateral knee swelling, which had responded to a short course of a nonsteroidal agent. At the time of her evaluation she was no longer taking any medication and had no access to insulin or other oral hypoglycemic agents.

Her medical history included a diagnosis of discoid lupus erythematosus made three years previously based on the findings of a skin biopsy and a serologic screen. The antinuclear antibody (ANA) titer was positive at a dilution of 1:64, and only antibodies to ribonucleoprotein were identified. Therapy was instituted with topical steroids and hydroxychloroquine (Plaquenil) sulfate for a short time.

The findings of a physical examination were within normal limits except for diffuse adenopathy. Laboratory values were normal for a complete blood count, platelet count, and erythrocyte sedimentation rate. A random glucose level was 59 mg per dl. Serum chemistry levels were normal except for an aspartate aminotransferase level of 47 IU per liter (normal 6 to 30), an alanine aminotransferase value of 55 IU per liter (6 to 45), and an alkaline phosphatase level of 393 IU per liter (64 to 238). The results of a urinalysis and thyroid function tests were normal. A serum screen was negative for oral hypoglycemic drugs.

The patient was admitted for a 72-hour fast, and serial glucose, insulin, C-peptide, and cortisol levels are shown in Table 1. Computed tomography of the abdomen revealed retroperitoneal adenopathy with no definite pancreatic abnormality. A lymph node biopsy specimen showed follicular cell hyperplasia. The patient was discharged without a definite diagnosis but, because of the presence of adenopathy, was thought to have a malignant lesion. She was instructed to eat frequently, including a nighttime snack.

A subsequent bone marrow biopsy specimen revealed trilineal hyperplasia and a single benign lymphoid aggregate. A second lymph node biopsy confirmed the presence of benign follicular hyperplasia, and a second computed tomographic scan of the abdomen was unchanged. The mild liver function test abnormalities persisted, and changes on serum protein electrophoresis were consistent with inflammation. With the institution of frequent feedings, the symptomatic episodes of hypoglycemia decreased in frequency but did not resolve completely.

Four months after the initial evaluation, arthritis of the hands, pleuritis, and low-grade fever developed. A second ANA titer was done and was 4+ positive at a dilution of 1:256 with a fine speckled pattern. Both anti-Sm and anti-ribonucleoprotein antibodies were identified. A complete blood count now showed leukopenia and lymphopenia. A diagnosis of active systemic lupus erythematosus was made based on the presence of a positive ANA titer and specific anti-Sm antibody, pleuritis, arthritis, and leukopenia. Initial therapy with nonsteroidal agents was unsuccessful, and the patient was placed on a regimen of prednisone, 20 mg daily, with the complete resolution of the laboratory abnormalities, fever, and symptoms of hypoglycemia.

Five months after starting steroid therapy, the patient had an increase in activity of her lupus marked by an increase in double-stranded DNA binding and decreased C3 and C4 levels. At seven months, she experienced neurologic symptoms consisting of transient aphasia and right arm numbness and tingling. Computed tomography of the head revealed moderate volume loss without focal findings. At this point the patient moved and is no longer followed at our institution. At no point after initiating steroid therapy did symptoms of hypoglycemia recur.

Antibodies to the insulin receptor were measured using the binding-inhibition assay. Briefly, aliquots of serum and cultured lymphocytes were suspended in plastic culture tubes, set up in duplicate. The cells are incubated for two hours at room temperature, and then the supernatant is discarded. Insulin labeled with iodine 125 is then added to the cells, and unlabeled insulin is added to one of each pair of duplicate tubes to estimate the nonspecific binding of ^{125}I-labeled insulin. After incubation for three hours at 15°C, cell-associated radioactivity is measured in a gamma counter.[11]

A serum specimen obtained before therapy contained in-

*The laboratory values in this case report were reported by various laboratories (see Table 1) in conventional units. We have not converted these values to Système International (SI) units as to do so introduces inconsistency (C-peptide values are not easily converted) and possible errors, such as with "insulin:glucose ratio."

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TABLE 1.—*Laboratory Data Obtained After a 72-Hour Fast**

Date	Time	Glucose, mg/dl	Insulin, μU/ml†	C-Peptide, ng/ml‡	Cortisol, μg/dl	Insulin: Glucose Ratio	Symptoms
Day 1	1700	43	12	0.7	..	0.28	No
Day 1	2200	42	2	0.3	..	0.05	No
Day 2	0100	41	2	0.5	7	0.05	No
Day 2	0330	35	3	0.4	12	0.09	No
Day 2	0530	36	2	0.4	17	0.06	No
Day 2	0920	24	5	0.5	23	0.21	Yes
Day 3	0600	78	..	...	13	....	No

*Due to the development of symptomatic hypoglycemia, the actual duration of fasting was only 20 hours.
†Insulin was measured by radioimmunoassay (Pharmacia Diagnostics, Uppsala Sweden) with a detection limit of <2 μU per ml.
‡C-peptide was measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles) with a detection limit of 0.07 ng per ml.

sulin-receptor antibodies that inhibited 54% of insulin binding to cultured lymphocytes at a 1:10 dilution of serum. A second serum specimen taken after her symptoms resolved and while she was receiving 5 mg of prednisone daily (three months after the initial specimen) contained no detectable insulin-receptor antibodies.

Discussion

Insulin-receptor antibodies were first described in 1976 in diabetic patients with type B extreme insulin resistance and acanthosis nigricans.[1] Subsequently, insulin-receptor antibodies have been reported in other disease states including Hashimoto's thyroiditis,[2] primary biliary cirrhosis,[3] progressive systemic sclerosis,[4] Sjögren's syndrome,[5] and systemic lupus erythematosus.[6-8] The presence of hypoglycemia due to insulin-receptor antibodies was first reported by Taylor and colleagues in 1982.[2] It has now been shown that the insulin-receptor antibodies have three biologic effects in vitro: they inhibit the binding of insulin to its receptor,[12] they simulate the effects of insulin on target tissues,[13] and they desensitize target tissues to insulin.[14] The ability of insulin-receptor antibodies to simulate insulin activity has been shown in vitro by the ability of antibody to stimulate the incorporation of glucose into glycogen and lipid.[2,13] Heterogeneity in the ability of anti-insulin-receptor antibody to block insulin action or mimic insulin activity has been reported.[13]

Harrison and Heyma in 1983 reported 18 documented cases of insulin-receptor antibodies.[15] Five patients were felt to have classic features of systemic lupus erythematosus. One patient presented with "reactive" hypoglycemia, and hypoglycemia developed in three patients during the course of their disease. It is not stated if these patients had features of systemic lupus. Also in 1983 Tardella and co-workers reported a case of anti-insulin-receptor antibodies and hypoglycemia in a patient with lupus nephritis.[6] The diagnosis of systemic lupus erythematosus was made three years and four months before the patient had symptoms of hypoglycemia. Moller and associates in 1986 reported the case of a patient who presented with acute hypoglycemic coma as her primary manifestation of systemic lupus.[7] This patient responded to therapy with prednisone.

The present case represents the second report of a patient with hypoglycemia due to insulin-receptor antibodies as an initial symptom of active systemic lupus erythematosus. Although the patient was diagnosed as having discoid lupus previously, she did not meet the criteria for a diagnosis of systemic lupus at that time. During the current presentation, systemic lupus erythematosus was confirmed by the presence of a positive antinuclear antibody screen and identification of the specific antibody to the Sm nuclear antigen, as well as arthritis, pleuritis, and lymphopenia.

This patient showed suppression of insulin levels in response to the development of hypoglycemia. The initial glucose value of 43 mg per dl with an insulin level of 12 μU per ml might suggest hyperinsulinism. The low C-peptide level in this specimen and the subsequent occurrence of insulin levels of 5 μU per ml or less with simultaneous C-peptide levels of less than 1.0 ng per ml effectively eliminates the possibility of hyperinsulinism. The presence of a slightly elevated insulin level in a patient with antibody to the insulin receptor has been previously described.[2] This patient was initially felt to have an insulinoma and underwent surgical treatment before the antibody to the insulin receptor was detected. Insulinoma should not be considered in the differential diagnosis of fasting hypoglycemia when insulin levels are suppressed.

The patient's hypoglycemic symptoms resolved, and the insulin-receptor antibody titer decreased with the institution of corticosteroid therapy. Similar responses to corticosteroid therapy have been reported.[2,3,7]

The presence of antibodies to the insulin receptor should be considered in any patient with unexplained hypoglycemia and features of autoimmunity or documented autoimmune disease. An early consideration of an autoimmune origin of the hypoglycemia may prevent invasive procedures and unnecessary surgical therapy.

REFERENCES

1. Kahn CR, Flier JS, Bar RS, et al: The syndromes of insulin resistance and acanthosis nigricans—Insulin-receptor disorder in man. N Engl J Med 1976; 294:739-745

2. Taylor SI, Grunberger G, Marcus-Samuels B, et al: Hypoglycemia associated with antibodies to the insulin receptor. N Engl J Med 1982; 307:1422-1426

3. Selinger S, Tsai J, Pulini M, et al: Autoimmune thrombocytopenia and primary biliary cirrhosis with hypoglycemia and insulin receptor autoantibodies—A case report. Ann Intern Med 1987; 107:686-688

4. Weinstein PS, High KA, D'Ercole AJ, et al: Insulin resistance due to receptor antibodies: A complication of progressive systemic sclerosis. Arthritis Rheum 1980; 23:101-105

5. Kawanishi K, Kawamura K, Nishina Y, et al: Successful immunosuppressive therapy in insulin resistant diabetes caused by anti-insulin receptor autoantibodies. J Clin Endocrinol Metab 1977; 44:15-21

6. Tardella L, Rossetti L, De Pirro R, et al: Circulating anti-insulin receptor antibodies in a patient suffering from lupus nephritis and hypoinsulinemic hypoglycaemia. J Clin Lab Immunol 1983; 12:159-165

7. Moller DE, Ratner RE, Borenstein DE: Systemic lupus erythematosus: Presentation as autoimmune hypoglycemia due to anti-insulin-receptor antibodies (Abstr). Clin Res 1986; 34:876A

8. Tsokos GC, Gorden P, Antonovych T, et al: Lupus nephritis and other autoimmune features in patients with diabetes mellitus due to autoantibody to insulin receptors. Ann Intern Med 1985; 102:176-181

9. Flier JS, Bar RS, Muggeo M, et al: The evolving clinical course of patients

with insulin receptor autoantibodies: Spontaneous remission or receptor proliferation with hypoglycemia. J Clin Endocrinol Metab 1978; 47:985-995

10. Dons RF, Havlik R, Taylor SI, et al: Clinical disorders associated with autoantibodies to the insulin receptor—Simulation by passive transfer of immunoglobulins to rats. J Clin Invest 1983; 72:1072-1080

11. Taylor SI, Underhill LH, Marcus-Samuels B: Assay of antibodies directed against cell surface receptors. Methods Enzymol 1985; 109:656-667

12. Flier JS, Kahn CR, Jarrett DB, et al: Characterization of antibodies to the insulin receptor: A cause of insulin-resistant diabetes in man. J Clin Invest 1975; 58:1442-1449

13. Kahn CR, Baird K, Flier JS, et al: Effects of autoantibodies to the insulin receptor on isolated adipocytes—Studies of insulin binding and insulin action. J Clin Invest 1977; 60:1094-1106

14. Taylor SI, Marcus-Samuels B: Anti-receptor antibodies mimic the effect of insulin to down-regulate insulin receptors in cultured human lymphoblastoid (IM-9) cells. J Clin Endocrinol Metab 1984; 58:182-186

15. Harrison LC, Heyma P: The receptor antibody diseases, *In* Davies TF (Ed): Autoimmune Endocrine Disease. New York, John Wiley & Sons, 1983, pp 101-125

Haloperidol-Induced Neuroleptic Malignant Syndrome in a 67-Year-Old Woman With Parkinsonism

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THE NEUROLEPTIC MALIGNANT SYNDROME (NMS) is generally described as a side effect of neuroleptic medications characterized by hyperthermia, autonomic nervous system dysfunction, skeletal muscle rigidity with elevated creatine kinase levels, and an altered mental state.[1] The prevalence of NMS has variously been reported to be 0.07% to 2.4%, with most figures being at about 1% of patients receiving neuroleptic medications.[2-7] Caroff in 1980 reported a mortality rate of 20%, attributed to respiratory failure due to pulmonary emboli or aspiration pneumonia, cardiovascular collapse due to autonomic instability, or acute renal failure due to myoglobinuria.[8] More recent reviews have yielded mortality rates from 4% to 22%.[9-13] Pearlman's review in 1986 suggested that the mortality had decreased to 4% in the last 50 reported cases at that time, probably due to a wider recognition.[10] All of these reports have been based on retrospective case reviews, rather than on prospective studies. Caroff's review also indicated that men are affected twice as often as women, with 80% being younger than 40 years. This has led to the conclusion that the syndrome generally occurs in young men. Several subsequent reviews have also indicated about a 2-to-1 predominance of NMS in men.[10,11] Addonizio reported an age range of 12 to 71 years, however, with a mean age of 40.[14] In this series only 51% were younger than 40. Furthermore, Addonizio also reported 18 cases of NMS in patients older than 60 years.[14] This supports the viewpoint that the syndrome is more common in elderly patients than previously thought.[15,16]

We report the case of a woman in her seventh decade diagnosed with NMS and briefly discuss the points of interest in this case in relationship to the current literature.

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Report of a Case

The patient, a 67-year-old woman, was admitted for a dementia evaluation, having had for the past six years a gradual, progressive memory loss resulting in placement at a nursing facility. At the time of admission, her husband was concerned about her increasing confusion and agitation, which had required medical management with haloperidol, 1 mg at bedtime, for approximately five months. In addition, a continuous "pill-rolling" tremor had developed over the past several weeks. On the initial examination, the patient was afebrile, and her blood pressure was 120/86 mm of mercury. Neurologically, she had masked facies, a "pill-rolling" tremor in her right hand with bilateral upper extremity cogwheel rigidity, and a shuffling gait. The initial impression was that of parkinsonism, idiopathic versus drug-induced. Further history revealed that most of her symptom complex preceded the use of low-dose haloperidol and favored a diagnosis of idiopathic parkinsonism with slowly progressive dementia.

Immediately after admission, the patient became increasingly more agitated, requiring additional intramuscular doses of haloperidol. On hospital day 1 she received a total of 12 mg with an additional 13 mg over the ensuing 48 hours. On hospital day 4 she was found by nursing staff to be minimally responsive, rigid, and incontinent, with a temperature of 40.5°C (104.9°F). Her blood pressure was 80/50 mm of mercury, and her pulse rate was 154 per minute. A Foley catheter was placed, and a urinalysis and subsequent culture showed no evidence of infection. A regimen of ampicillin and gentamicin sulfate was started empirically, and she was transferred to an intensive care setting where a sepsis workup, including throat, urine, sputum, blood, and cerebrospinal fluid studies, was negative. A leukocyte count was elevated at 19.1×10^9 per liter. A creatine kinase level was elevated at 2,381 U per liter with an MB fraction of 0.04. Head computed tomography and abdominal ultrasonography were negative. An electrocardiogram and a technetium Tc 99m pyrophosphate myocardial scan showed no evidence of acute ischemic changes or damage. A regimen of dopamine hydrochloride, 3 to 5 μg per kg of body weight per minute, was started for inotropic support. On the following day, the fever rapidly subsided to 38.4°C (100.1°F) and the creatine kinase value declined to 1,691 U per liter. Over the next several days, the defervescence continued and she no longer required dopamine for blood pressure support.

On hospital day 5, the antibiotic therapy was discontinued and her condition had returned to that of her baseline examination, although she was clearly left in a weakened state, requiring assistance with ambulation. On the ninth hospital day, her urine output deteriorated, causing concern about acute renal failure. Her temperature was 37.2°C (99.0°F). A urinalysis showed 30 to 40 leukocytes and 10 to 20 erythrocytes per high-power field, and the Foley catheter was removed. A subsequent urine culture grew *Escherichia coli,* and her urine output improved with a regimen of norfloxacin, 500 mg twice a day, and intravenous hydration.

During this time, a regimen of 10 mg of carbidopa and 100 mg of levodopa (Sinemet 10-100) three times a day was started, and her tremor was found to rapidly abate. A psychiatric consultation was obtained regarding continuing medi-